AD_____

Award Number: DAMD17-98-1-8321

TITLE: Viral Vectors Selective for Metastatic Breast Cancer Tumor Cells

PRINCIPAL INVESTIGATOR: William Folk, Ph.D.

CONTRACTING ORGANIZATION: University of Missouri
Columbia, Missouri 65211

REPORT DATE: November 1999

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for public release
distribution unlimited

The views, opinions and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy or decision unless so designated by other documentation.

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 074-0188

1. AGENCY USE ONLY (Leave blank)	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	November 1999	Annual (01 Oct 98 - 01 Oct 99)

4. TITLE AND SUBTITLE
Viral Vectors Selective for Metastatic Breast Cancer Tumor Cells

5. FUNDING NUMBERS
DAMD17-98-1-8321

6. AUTHOR(S)
William Folk, Ph.D.

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
University of Missouri
Columbia, Missouri 65211

e-mail:
folkw@missouri.edu

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSORING / MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for public release
distribution unlimited

12b. DISTRIBUTION CODE

13. ABSTRACT *(Maximum 200 Words)*

Breast cancer is the most common malignancy in American women, and its most life-threatening aspect is metastasis. There are presently no effective means to treat metastatic cancer, and novel therapies are required to eliminate metastatic cells and the consequent morbidity and mortality of breast cancer.

We are developing polyomavirus gene therapy vectors which are capable of specifically targeting metastatic breast cancer cells. Selective targeting will result from the specific attachment of modified viruses to urokinase plasminogen activator (uPA) expressed on metastatic cells and to the selective expression of genes under the control of promoters which are preferentially activated in metastatic cells. These gene therapy vectors will be assembled from highly purified capsid proteins, histones and DNA and will be tested in human breast cancer cells in culture and in tumors.

During the past year, we have modified the polyomavirus VP1 capsid protein to contain sequences of uPA capable of binding to the uPA receptors on tumor cells. We have obtained the requisite enzymes for assembling DNA into chromatin. The next year will be devoted to assembling virus-like particles with the modified capsid proteins and the chromatin, and to preparing to test them for specificity of adsorption to cancer cells.

14. SUBJECT TERMS
Breast Cancer, IDEA

15. NUMBER OF PAGES
6

16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
Unclassified	Unclassified	Unclassified	Unlimited

NSN 7540-01-280-5500

Standard Form 298 (Rev. 2-89)
Prescribed by ANSI Std. Z39-18
298-102

FOREWORD

Opinions, interpretations, conclusions and recommendations are those of the author and are not necessarily endorsed by the U.S. Army.

_____ Where copyrighted material is quoted, permission has been obtained to use such material.

_____ Where material from documents designated for limited distribution is quoted, permission has been obtained to use the material.

_____ Citations of commercial organizations and trade names in this report do not constitute an official Department of Army endorsement or approval of the products or services of these organizations.

__✓__ In conducting research using animals, the investigator(s) adhered to the "Guide for the Care and Use of Laboratory Animals," prepared by the Committee on Care and use of Laboratory Animals of the Institute of Laboratory Resources, national Research Council (NIH Publication No. 86-23, Revised 1985).

_____ For the protection of human subjects, the investigator(s) adhered to policies of applicable Federal Law 45 CFR 46.

_____ In conducting research utilizing recombinant DNA technology, the investigator(s) adhered to current guidelines promulgated by the National Institutes of Health.

_____ In the conduct of research utilizing recombinant DNA, the investigator(s) adhered to the NIH Guidelines for Research Involving Recombinant DNA Molecules.

_____ In the conduct of research involving hazardous organisms, the investigator(s) adhered to the CDC-NIH Guide for Biosafety in Microbiological and Biomedical Laboratories.

Oct 27 '99

PI - Signature Date

Table of Contents

Introduction

The most life-threatening aspect of cancer is its capacity to invade normal tissue and to establish new foci of tumor cells at distant sites. While there has been some progress in understanding some of the genetic and cellular mechanisms involved in the conversion of normal cells to metastatic tumor cells, little progress has been made in utilizing what has been learned of the molecular mechanisms of metastasis to reduce its impact upon morbidity and mortality. The objective of this work is to do that by developing novel gene therapy vectors selective for metastatic cells. Selectivity of the gene therapy vectors will rely upon metastatic cells expressing receptors to which the vectors can adsorb and upon the metastatic cells expressing signal transduction pathways which will activate vector gene expression.

Key Research Accomplishments — Reportable Outcomes

We are making the progress planned and described in the original application. Specifically:

Technical Objective 1:

We have constructed a polyomavirus vector with the firefly luciferase gene under the control of the viral enhancer and the viral promoters.

Technical Objective 2:

We have modified the polyomavirus VP1 protein to contain high affinity ligands for the uPA receptor. These are being expressed in *E. coli* and will then be placed in vectors capable of expression in insect cells. We will then measure the efficiency of capsomere formation and optimize capsid assembly with these proteins.

Technical Objective 3:

We have obtained the enzymatic machinery required to reconstruct chromatin with DNA containing the LUC gene under the control of the viral enhancer and during the next year will use it to reconstitute chromatin.